the cyclodextrin monomer precursor is disubstituted with the same or different leaving group, with a comonomer A precursor capable of displacing the leaving groups to form a linear cyclodextrin copolymer having a repeating unit of formula Ia, Ib, or a combination thereof.

At the Interview Examiner Crane explained how he considered Applicants' claimed linear cyclodextrin copolymers to represent a distinct genus from Applicants' claimed linear cyclodextrin copolymers having ring opened and oxidized cyclodextrin monomers. Examiner Crane suggested pursuing separate independent claims to each of these genuses. In view of this suggestion Applicants have cancelled the claims drawn to linear cyclodextrin copolymers having ring opened and oxidized cyclodextrin monomers. Examiner Crane also indicated that separating the generic claims in this manner would make clear the subject matter claimed. Examiner Crane also indicated that the trapeziodal generic structures of the claims are clear following this amendment. See the Examiner's remarks on pages 4 and 5 of the Office Action. Because canceling the claims is merely intended to separate what the Examiner considers to be mutually exclusive genuses, this differentiation between claims does not affect the scope or range of equivalents for the claimed subject matter.

With regard to claims 6 and 30, the Examiner has noted that some amine functions within the Markush group of comonomer A's are protonated while some are not protonated. Applicants have amended claims 6 and 30 to recite this feature already present in the claims as originally written. In amended claims 6 and 30, A is a protonated or non-protonated comonomer selected from the group consisting of: ..." Protonated and non-protonated linear cyclodestrin polymers are shown in Applicants' examples.

With regard to claim 7, the Examiner considers the term "A is biodegradable or acid-labile" is functional language not easily translatable into specific chemical structures, thereby rendering the metes and bounds of the instant claim indefinite. Comonomer A is a monomer unit of formula Ia or Ib that upon polymerization with cyclodextrin C form Applicants' claimed linear cyclodextrin copolymer. The terms "biodegradable" and "acid-labile" are terms of art meaning that the linear cyclodextrin copolymer could be cleaved within a comonomer A via biodegradation or addition of acid. See, for example, pages 25 and 26 of the specification.

With regard to claims 9, 10, and 31, the Examiner considers the term "at least one ligand is bound to the linear cyclodextrin copolymer" to imply subject matter ("ligand") which is open to various interpretations. As discussed at the Interview, the "ligand" allows the linear cyclodextrin polymer to target and bind to a cell. This is discussed on page 16 of the specification. The term "ligand" and a ligand's function, as SPE Hutzell discussed at the interview, is well known in the art.

The Examiner notes that claim 18 recites a therapeutic composition. As discussed at the Interview, Applicants' linear cyclodextrin copolymers are useful in drug deleivery. See page 27 of the Specification. The Examiner indicated that the terminology "therapeutic composition" was acceptable.

## III. The Obviousness-type Double Patenting Rejections

Claims 18, 44, and 46 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-20 of copending application Application No. 09/453,707. Allowable subject matter has not indicated in these applications. Applicants respectfully request these obviousness-type double patenting rejections be held in abeyance until the indication of allowable subject matter in these applications.

## IV. The Rejection under 35 U.S.C. § 102(e) over Bachmann *et al.*

Claims 1-2, 7-18, 24, 31, 37, and 44 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Bachmann *et al.* '768 ("Bachmann"). Applicants respectfully traverse this rejection.

The Examiner refers Applicants to the '768 patent's abstract which refers to "biomedical articles," to column 3, lines 35-39, to column 5, lines 32-36, to column 7, lines 1-3, and to column 7, lines 19-23 and associated explanatory text as containing subject matter which reads directly on the instant claims including "oxidized" cyclodextrins as being an obvious variation following from contact with hydrogen peroxide in the presence of metal ions, a mixture well known to generate hydroxyl radicals, a known oxidizing agent.

Applicants' claimed invention relates to a linear cyclodextrin copolymer containing repeating units of formula (Ia), (Ib), or combination thereof. As a result of having of having repeating units of formula (Ia) or (Ib), the resulting linear cyclodextrin copolymer has more than one cyclodextrin moiety within the polymer backbone chain. As discussed below, Bachmann fails to teach or suggest a polymer having more than one cyclodextrin moiety, unoxidized or oxidized, in the polymer chain backbone. Thus, Bachmann fails to teach or suggest Applicants' claimed invention.

Bachmann describes polymerizable derivatives of carbohydrates comprising a compound of formula (I):

$$R^1—(COO—Alk)_m—(OCONH—R)_n—(NHCO)_pY—Z \qquad (I)$$

In formula (I), the only cyclodextrin mentioned is in variable "Z." Abstract, and Col. 2, lns.19-32. Bachmann defines "Z" as follows:

> ...Z is a monovalent radical, minus a single hydroxy group, of a mono-, di- or tri-saccharide, of an oligosaccharide, of a cyclodextrin (CD) or of an anhydrosaccharide;...

Col. 2, lns. 30-32. Since Z is a monovalent radical, it is bound to the rest of Bachmann's compound at only one position. Thus, as shown by Bachmann's formula (I), Z terminates the portion of the compound of formula (I) attached to R', "a radically polymerizable hydrocarbon group." Col. 2, ln. 24. Being terminal group, Z would not be a repeating unit of the polymer backbone chain upon polymerization of R'. Thus, when Z is a monovalent radical, minus a single hydroxy group, of a cyclodextrin, only a single cyclodextrin moiety would exist and that cyclodextrin moiety would not be within the polymer backbone chain. Furthermore, R' by definition as a "radically polymerizable hydrocarbon group" would not contain a cyclodextrin group. Thus Bachmann would not teach or suggest a polymer having cyclodextrin within the polymer backbone as in Applicants' claimed linear cyclodextrin copolymers. Thus, Bachmann neither anticipates nor renders obvious Applicants' claimed invention. Applicants respectfully request the rejection under 35 U.S.C. § 102(e) be withdrawn.



B

## IV. The Rejection Under 35 U.S.C. § 102(b) over Tabushi *et al.*

Claims 1-3, 7-18, 24, 26, 27, 31, 37, 44, and 46 are rejected under 35 U.S.C. § 102(b) as being anticipated by Tabushi *et al.* The Examiner refers Applicants to p. 1919, Scheme I and Table 1, item 5e, relying on this as disclosing a synthesis and product which reads on the instant process and product-by-process claims. Applicants respectfully traverse this rejection.

As discussed above, Applicants' claimed invention relates to linear cyclodextrin copolymers, a method of their preparation, and their use in therapeutic compositions. Tabushi relates to articifical receptors used in chromatographic columns. More specifically, Tabushi discloses cyclodextrin derivatives immobilized on polymer beads used in chromatographic columns. Tabushi, p. 1918. Item 5e in Table I to which the Examiner refers is an elution fraction from Tabushi's chromatographic column. Tabushi, with cyclodextrin derivatives immobilized onto polymer beads, does not teach or suggest a linear cyclodextrin copolymer as recited in Applicants' claims. Nothing in Tabuchi teaches or suggests the linear cyclodextrin copolymers of Applicants' claimed invention. Tabushi, therefore, does not anticipate, nor would it render obvious Applicants' invention. Applicants respectfully request this rejection under § 102(b) be withdrawn.

## VII. Objection to the Disclosure

As expressed on page 11, lines 1-7 of the Office Action, the disclosure is objected to because of the following formalities:

> at pages 42 and 44, last line of both, the structural representations incorporating a schematic "cyclodextrin" appear to contain pentavalent carbons. The same problem occurs at p. 48.

## VII. Conclusion

Applicants respectfully request reconsideration of the subject application in view of the above remarks. The subject application is now in condition for allowance and early notice to that effect is respectfully solicited.

**EXCEPT** for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully submitted,

**MORGAN, LEWIS & BOCKIUS LLP**

By: 
Jeffrey A. Lindeman
Reg. No. 34,658

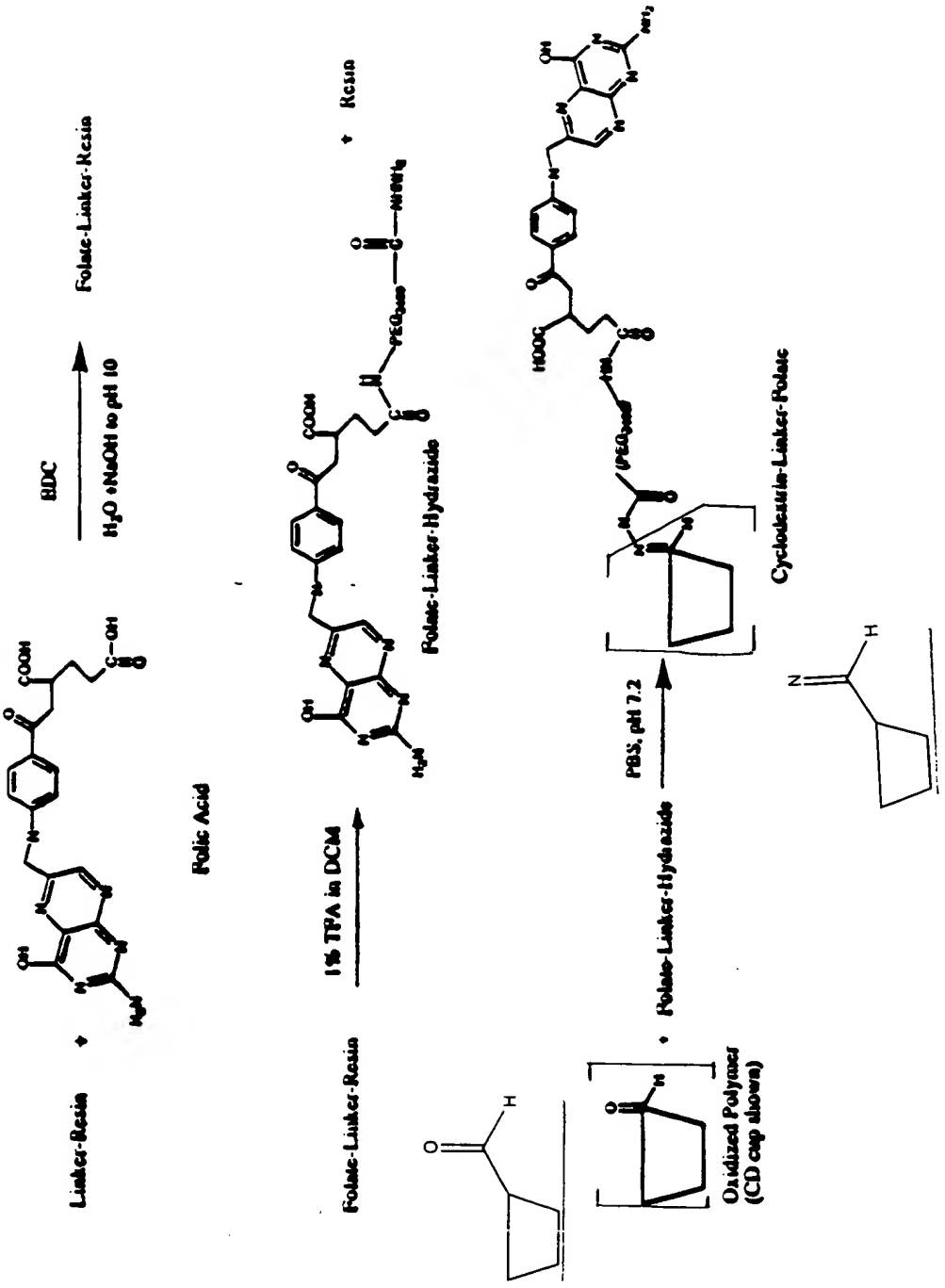
Dated: August 1, 2001

**CUSTOMER NO. 009629**
**MORGAN, LEWIS & BOCKIUS LLP**
1800 M Street, N.W.
Washington, D.C. 20036
(202) 467-7746
(202) 467-7176 (Fax)



B

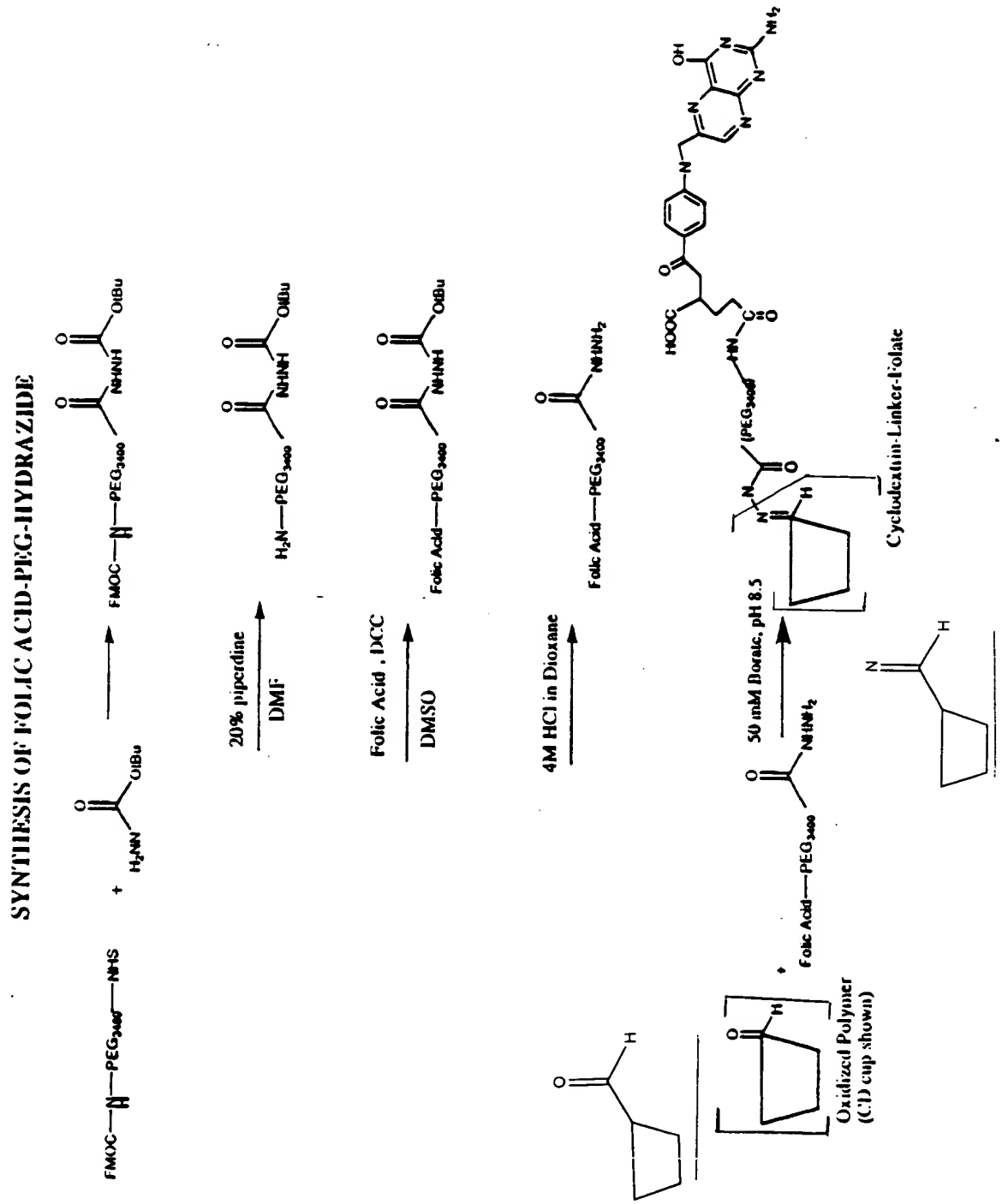
EXHIBIT A



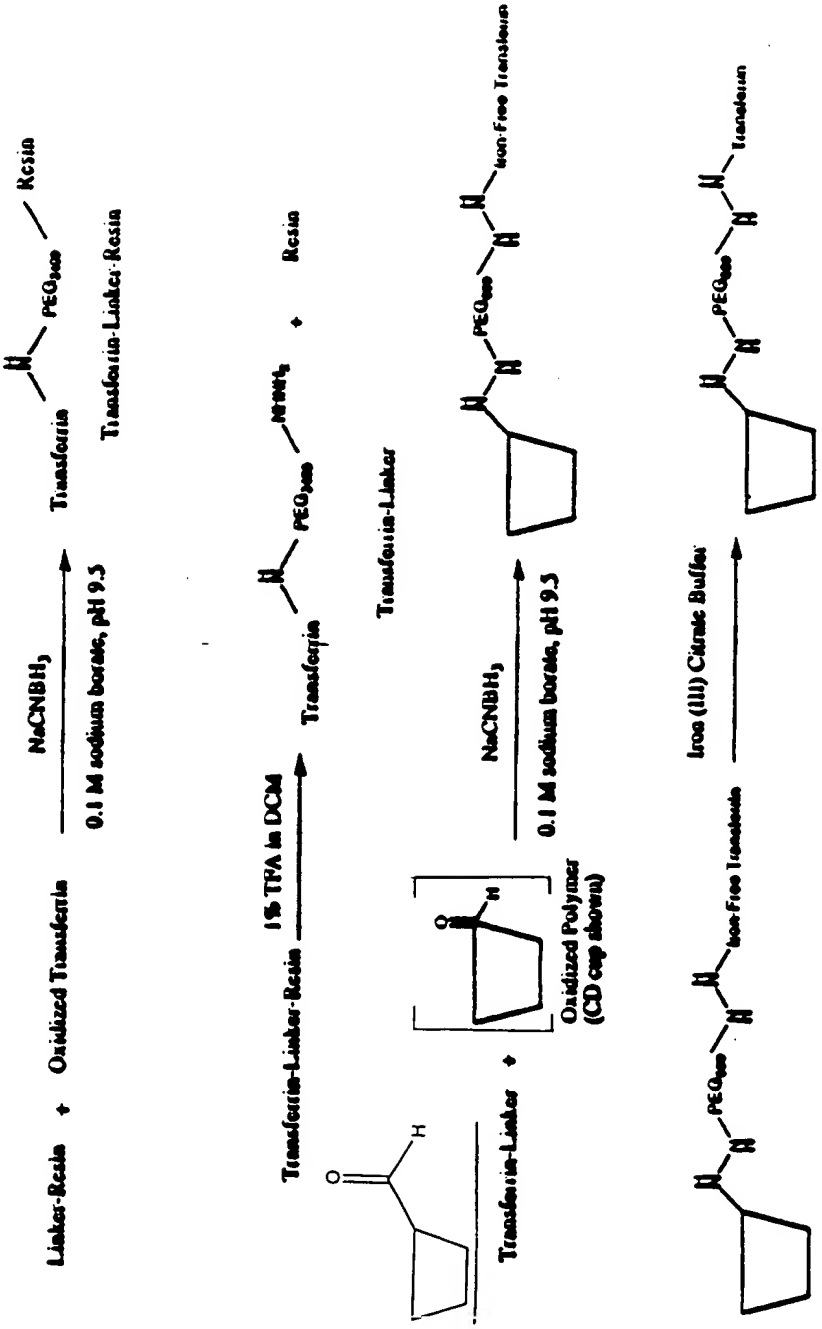




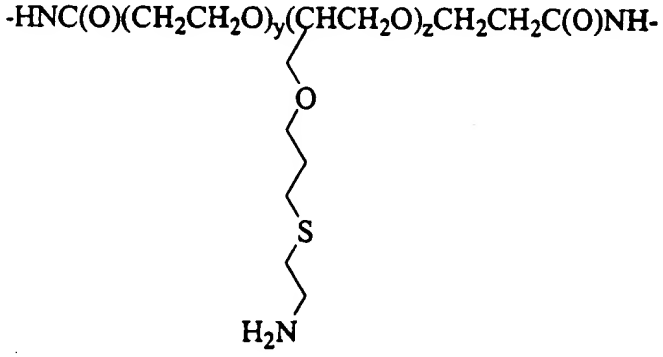

B

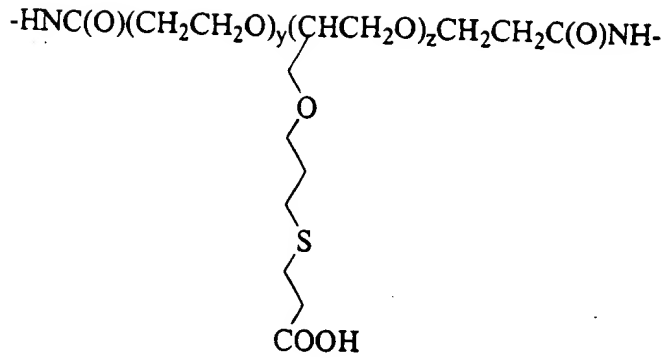

SYNTHESIS OF FOLIC ACID-PEG-HYDRAZIDE
FMOC—NH—PEG3400—NHS
+
H2NNH
OtBu
FMOC—NH—PEG3400—NHNH
20% piperdine
DMF
H2N—PEG3400—NHNH
Folic Acid , DCC
DMSO
Folic Acid—PEG3400—NHNH
4M HCl in Dioxane
Folic Acid—PEG3400—NHNH2
50 mM Borate, pH 8.5
Oxidized Polymer
(CD cap shown)
Cyclodextrin-Linker-Folate

**TRANSFERRIN ATTACHMENT TO CYCLODEXTRIN POLYMER**



6. (Amended) A cyclodextrin copolymer of claim 1, wherein A is a protonated or non-protonated comonomer selected from the group consisting of:-$HNC(O)(CH_2)_xC(O)NH$-, -$HNC(O)(CH_2)_xSS(CH_2)_xC(O)NH$-,
-$^+H_2N(CH_2)_xSS(CH_2)_xNH_2^+$-, -$HNC(O)(CH_2CH_2O)_xCH_2CH_2C(O)NH$-,
-$HNNHC(O)(CH_2CH_2O)_xCH_2CH_2C(O)NHNH$-, -$^+H_2NCH_2(CH_2CH_2O)_xCH_2CH_2CH_2NH_2^+$-,
-$HNC(O)(CH_2CH_2O)_xCH_2CH_2SS(CH_2CH_2O)_xCH_2CH_2C(O)NH$-,
-$HNC(NH_2^+)(CH_2CH_2O)_xCH_2CH_2C(NH_2^+)NH$-,
-$SCH_2CH_2NHC(NH_2^+)(CH_2)_xC(NH_2^+)NHCH_2CH_2S$-,
-$SCH_2CH_2NHC(NH_2^+)(CH_2)_xSS(CH_2)_XC(NH_2^+)NHCH_2CH_2S$-,
-$SCH_2CH_2NHC(NH_2^+)CH_2CH_2(OCH_2CH_2)_xC(NH_2^+)NHCH_2CH_2S$-,

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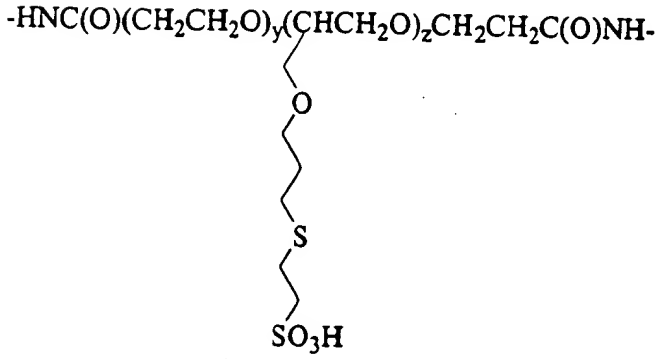
O
S
COOH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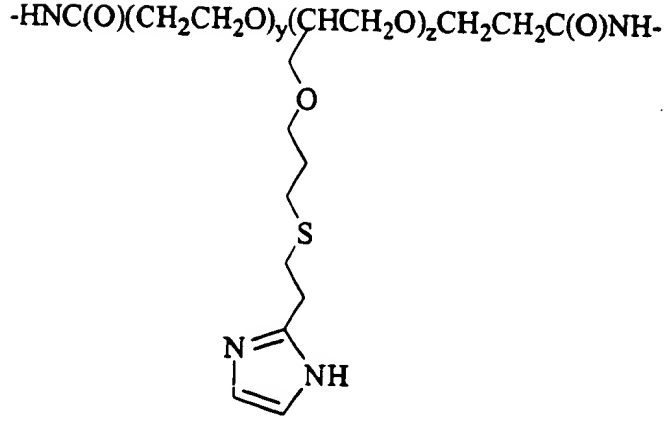
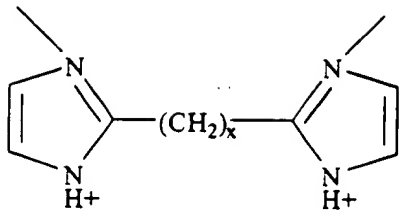
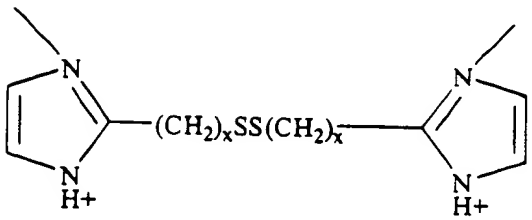
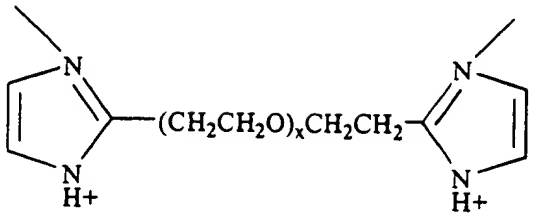
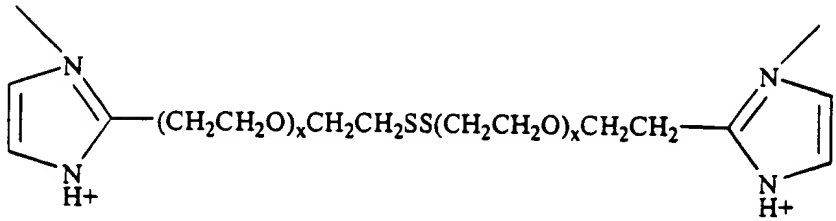
S
SO3H

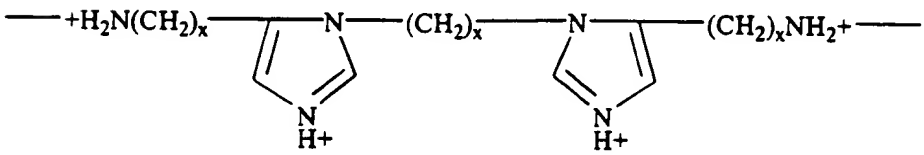

-HNC(O)(CH2CH2O)y(CHCH2O)zCH2CH2C(O)NH-
O
S
N
NH

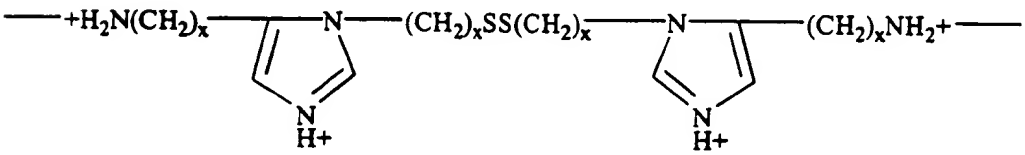


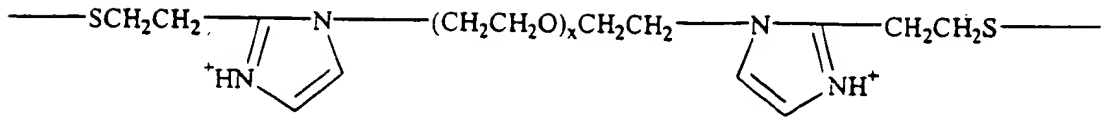








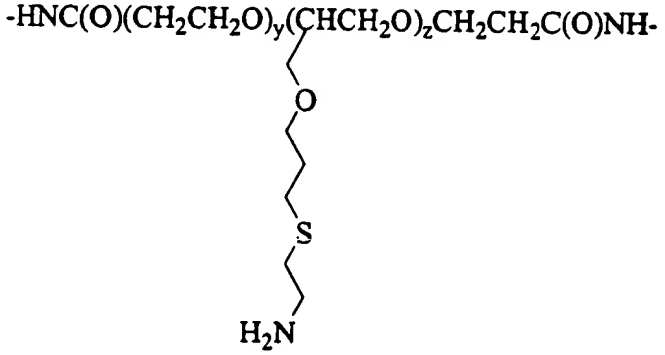


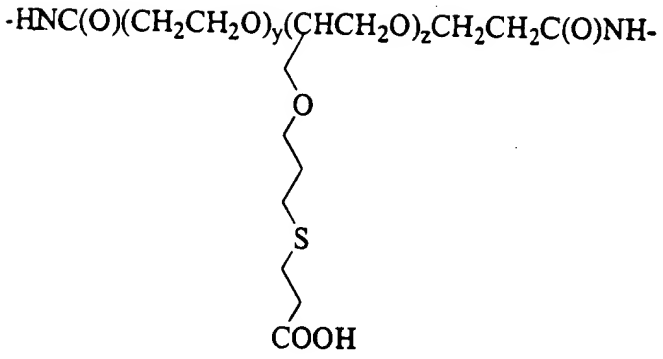
and 

where x = 1-50, and y+z=x.

18. (Amended) A therapeutic composition comprising a cyclodextrin copolymer of claim 1, 8, 9, or 10[, 11, 13, 14 or 15] and a therapeutic agent.

30. (Amended) A method of claim 24, wherein A is a protonated or non-protonated comonomer selected from the group consisting of:-$HNC(O)(CH_2)_xC(O)NH$-, -
$HNC(O)(CH_2)_xSS(CH_2)_xC(O)NH$-,
-$^+H_2N(CH_2)_xSS(CH_2)_xNH_2^+$-, -$HNC(O)(CH_2CH_2O)_xCH_2CH_2C(O)NH$-,
-$HNNHC(O)(CH_2CH_2O)_xCH_2CH_2C(O)NHNH$-, -$^+H_2NCH_2(CH_2CH_2O)_xCH_2CH_2CH_2NH_2^+$-,
-$HNC(O)(CH_2CH_2O)_xCH_2CH_2SS(CH_2CH_2O)_xCH_2CH_2C(O)NH$-,
-$HNC(NH_2^+)(CH_2CH_2O)_xCH_2CH_2C(NH_2^+)NH$-,
-$SCH_2CH_2NHC(NH_2^+)(CH_2)_xC(NH_2^+)NHCH_2CH_2S$-,
-$SCH_2CH_2NHC(NH_2^+)(CH_2)_xSS(CH_2)_XC(NH_2^+)NHCH_2CH_2S$-,
-$SCH_2CH_2NHC(NH_2^+)CH_2CH_2(OCH_2CH_2)_xC(NH_2^+)NHCH_2CH_2S$-,

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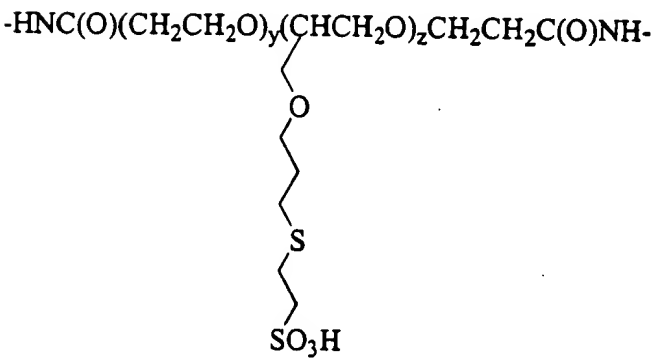
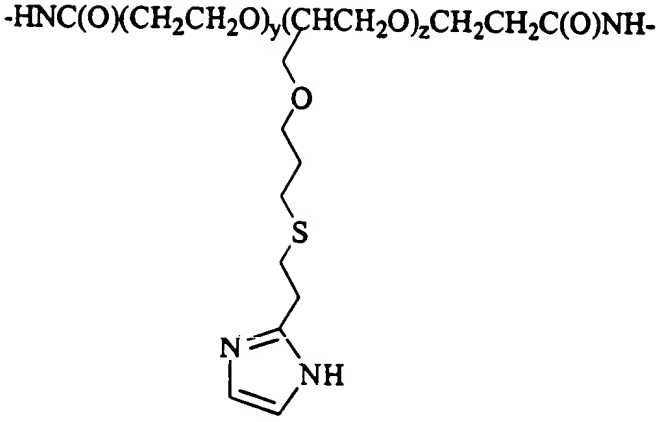
O
S
COOH


-HNC(O)(CH2CH2O)y(CHCH2O)zCH2CH2C(O)NH-
O
S
SO3H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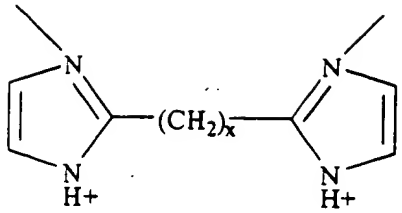
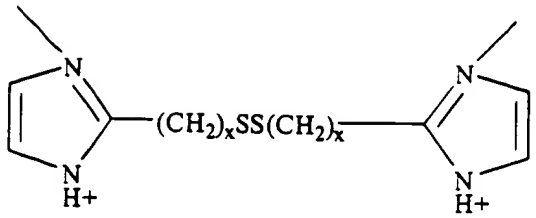
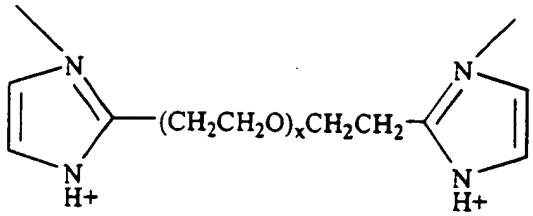
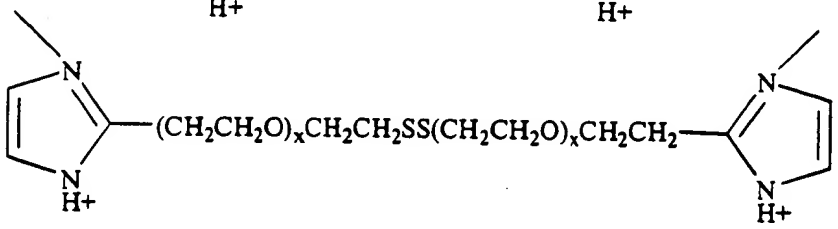
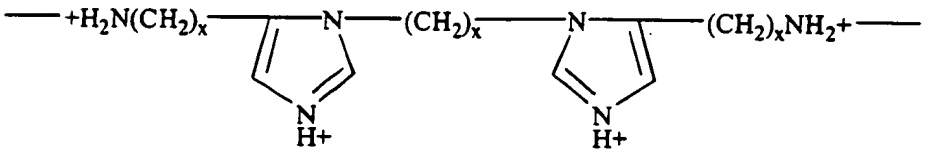
O
S
N
NH

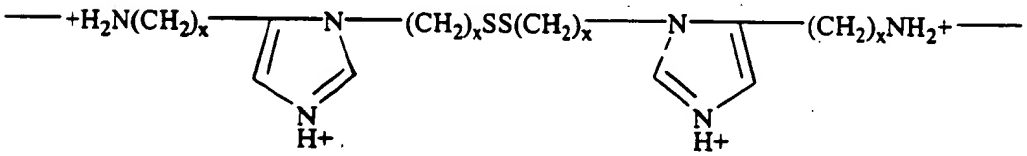




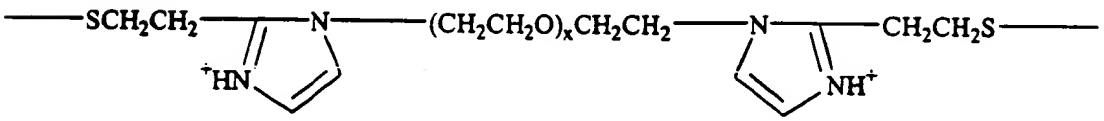








and



where x = 1-50, and y+z=x.

46. (Amended) A method of delivering a therapeutic agent comprising the steps of:

combining a cyclodextrin copolymer of claims 1, 8, 9, or 10, [11, 13, 14 or 15] with a therapeutic agent to form a mixture; and

allowing said mixture to self-assemble to form an associated composition; and

administering a therapeutically effective amount of said associated composition to a subject in need of said therapeutic agent.

47. (New) A linear cyclodextrin copolymer comprising substituted or unsubstituted, cyclodextrin moieties bifunctionally bound in the linear copolymer backbone, through the number 2, 3, or 6 position of at least one glucopyranose ring of the cyclodextrin, to bifunctional moieties linking the cyclodextrins of the linear cyclodextrin polymer.

48. (New) A linear cyclodextrin copolymer of claim 1, 8, 9, 10, or 47 wherein said linear cyclodextrin copolymer is water soluble.

50. (New) A therapeutic composition comprising a cyclodextrin copolymer of claim 48 and a therapeutic agent.

50. (New) A method of treatment comprising the step of administering a therapeutically effective amount of a therapeutic composition of claim 48.

55. (New) A cyclodextrin copolymer of claim 48, wherein at least one ligand is bound to the linear cyclodextrin copolymer.

52. (New) A method of treatment comprising the step of administering a therapeutically effective amount of a therapeutic composition of claim 50.

56. (New) A therapeutic composition comprising a cyclodextrin copolymer of claim 47 and a therapeutic agent.

57. (New) A method of treatment comprising the step of administering a therapeutically effective amount of a therapeutic composition of claim 47.

58. (New) A cyclodextrin copolymer of claim 47, wherein at least one ligand is bound to the linear cyclodextrin copolymer.

55. (New) A method of treatment comprising the step of administering a therapeutically effective amount of a therapeutic composition of claim 54.